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Pulmonary Impedance in Dogs Measured by Forced Random Noise with a Retrograde Catheter

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16. ABSTRACT

Retrograde catheter and forced random noise techniques were combined to study the distribution of resistance and compliance in dogs following the inhalation of aerosols containing 2.5 and 5.0 mg/ml of histamine.

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JOURNAL ARTICLE

Pulmonary impedance in dogs measured by forced random noise with a retrograde catheter

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FULLTON, J. M., D. A. HAYES, AND R. L. PIMMEL. *Pulmonary impedance in dogs measured by forced random noise with a retrograde catheter.* J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 52(3): 725–733, 1982.—Retrograde catheter and forced random noise techniques were combined to study the distribution of resistance and compliance in dogs following the inhalation of aerosols containing 2.5 and 5.0 mg/ml of histamine. Mean base-line peripheral resistance was 0.367 $cmH_2O \cdot l^{-1} \cdot s$, agreeing with previous estimates. After correction for the endotracheal tube, the mean central airway resistance was 0.040 $cmH_2O \cdot l^{-1} \cdot s$, considerably lower than previous estimates. This discrepancy was attributed to an overcorrection for the endotracheal tube resistance. The lower histamine dose caused a substantial increase in peripheral resistance, a relatively small increase in central resistance, and substantial decreases in total and peripheral compliance. After the higher histamine dose, changes in peripheral resistance and both compliances were similar to those obtained with the lower dose; however, the increase in central resistance was much larger than at the lower dose. The difference between total and peripheral compliance yielded estimates of airway compliance of 0.00306 l/cmH_2O before and 0.00104 l/cmH_2O after 2.5 mg/ml of histamine.

respiratory resistance; respiratory compliance; airway compliance; central resistance; peripheral resistance; histamine exposure; airway reactivity

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THE RETROGRADE CATHETER technique has been used to study the distribution of resistance in the lung and the effect of various interventions on this distribution (12, 13, 17, 18, 31, 32, 33). In general measurements are made using single-frequency forced oscillations, and some questions have been raised concerning the reliability of these measurements (12). The forced random noise approach for characterizing impedance may overcome these difficulties, because measurements are averaged over several frequencies and over several time intervals, and because many of the measurements are away from the resonant frequency. In addition, the forced random noise technique provides simultaneous estimates of compliance as well as resistance. We have therefore used random noise in conjunction with a retrograde catheter technique to study the distribution of respiratory resistance and compliance in dogs and the effect of inhaled histamine on these parameters.

METHODS

Eight mongrel dogs (18–22 kg) were induced with methohexital sodium (3 mg/kg), anesthetized with chloralose (80 mg/kg) and urethan (800 mg/kg), intubated with an 8.5-mm cuffed endotracheal tube (Rusch), and ventilated mechanically with a Harvard Apparatus model-607 ventilator. Supplementary doses of chloralose and urethan were administered as required to maintain anesthesia. Chloralose and urethan were used as the anesthetic because pentobarbital sodium may inhibit reflex bronchoconstriction in dogs (14). An intravenous saline drip was administered throughout the experiment, and an arterial line was placed to monitor blood pressure and to obtain periodic samples of arterial blood for determination of arterial blood gases. A rectal probe (Yellow Springs Instrument) was used to monitor body temperature, and a heating pad was applied to maintain body temperature.

Forced random noise measurements of total respiratory impedance (including the impedance of the endotracheal tube) were made using the apparatus shown in Fig. 1. A random pressure signal, band limited to approximately 20 Hz, was generated by a special noise generator (8) and used to drive an Acoustic Research AR3 loudspeaker. This random pressure fluctuation was coupled to the animal's respiratory system through a screen pneumotachometer (Hans-Rudolph model 3700) via the endotracheal tube. The pressure drop across the pneumotachometer screen was measured with a Validyne MP-45 pressure transducer to detect the induced random flow signal. The pressure at the entrance to the endotracheal tube was coupled through 15 cm of PE-200 tubing to another Validyne MP-45 to detect the applied random pressure signal. The amplitude and phase response of the pressure and flow measurement system were verified up to 20 Hz. Prior to each experiment, the transducers were calibrated with a water manometer and standard rotameter and the calibration signals were recorded on magnetic tape using an FM recorder (Hewlett-Packard 3968A).

Just before each measurement the animal was hyperventilated with normal tidal volumes to avoid hyperinflation. With the animal apneic at functional residual capacity (FRC), a 45-s record of the random pressure and flow signals was recorded on magnetic tape while the same signals were monitored on an oscilloscope (Tektronix 5113). The recorded signals were processed off-line to obtain closed-chest total respiratory impedance data as described below.

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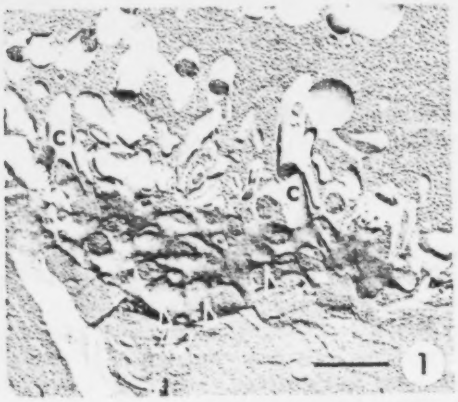


Fig. 1. Freeze-fracture preparation of normal human nasal epithelium. Mature emergent cilia (C) and ciliary necklaces are visible. The fractured portion of the lumenal membrane contains several patches of particles (arrows) which will become ciliary necklaces of newly emergent cilia. Bar = 1.0 μm.

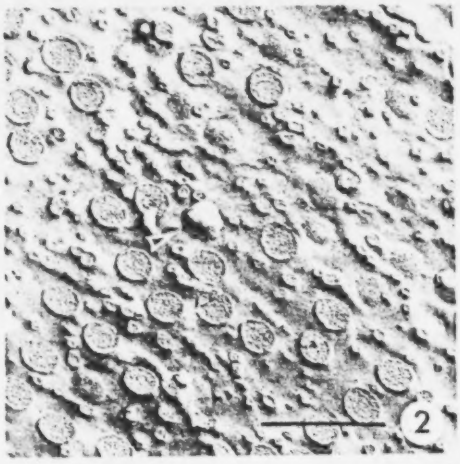
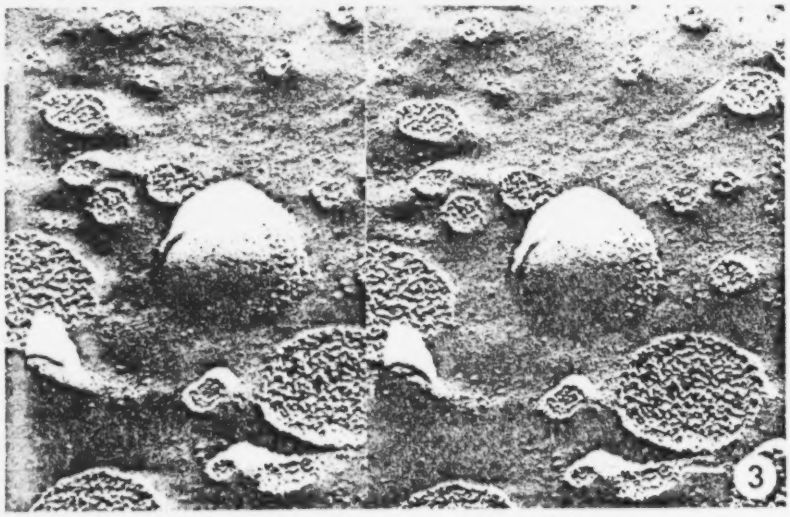


Fig. 2. Electron micrograph surveying a ciliated nasal epithelial cell lumenal membrane. The developmental sequence of new ciliary necklaces from patches of membrane associated particles can be observed. A new cilium (arrow) emerging through the lumenal membrane can be seen. This cilium is also shown in the stereo pair in Fig. 3 below. Bar = 1.0 μm.

Fig. 3. Stereo pair of emergent cilium. Particles comprising the new ciliary necklace can be seen at its base. Bar = 0.1 μm.



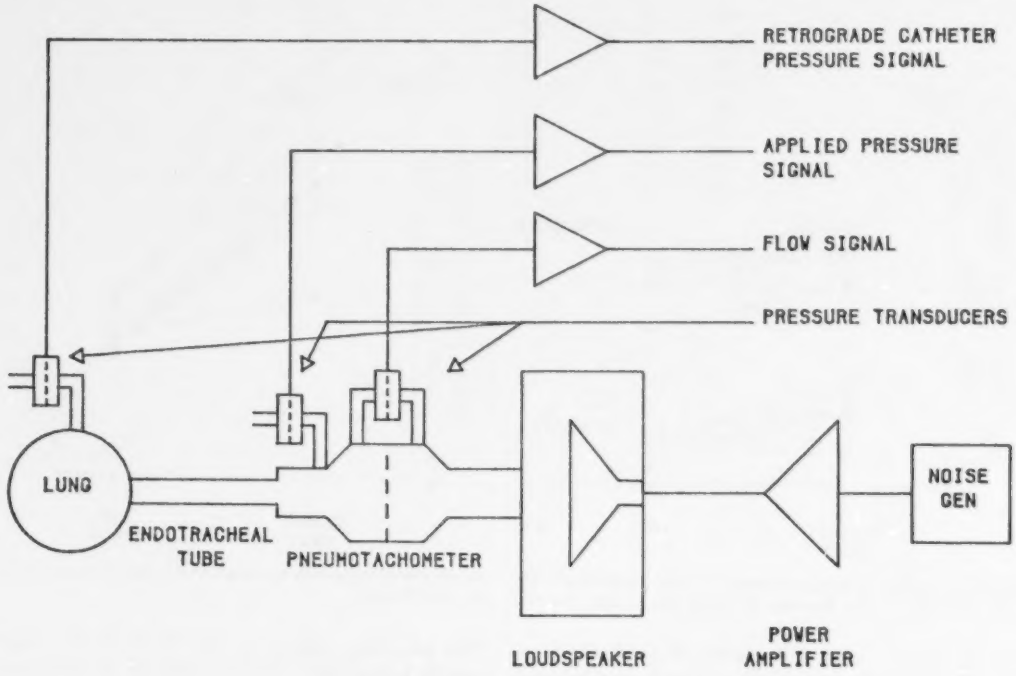


FIG. 1. Block diagram of experimental apparatus.

After recording closed-chest data, the chest was opened through a sternum-splitting incision and retracted widely. The animals were mechanically ventilated using 5 cmH_2O of positive end-expiratory pressure throughout the remainder of the study. A second record of the random pressure and flow data was recorded at this transpulmonary pressure. After recording the open-chest base-line data, a 100-cm PE-200 retrograde catheter with a 2- to 3-mm flange was inserted over a piano-wire guide introduced through a flexible plastic tube in a manner similar to that described by Macklem and Mead (17). After the catheter was pulled snug and wedged, it was cut to a length of 15 cm to match the length of the tubing used to measure the total pressure at the airway opening. The retrograde catheter was connected to a third Validyne MP-45 pressure transducer, which had been calibrated and characterized as previously described. When not being used for measurements the retrograde catheter was kept patent by a small airflow, typically 5 ml/min.

Once the retrograde catheter was in place, approximately 45 s of data from the three transducers (flow, total pressure, and peripheral pressure) were recorded simultaneously on the tape recorder for later analysis. These signals were recorded with the animal apneic after hyperventilation without hyperinflation and with a resting transpulmonary pressure of 5 cmH_2O. The pressure signals were monitored on the oscilloscope throughout the recording interval to assure that the peripheral pressure signal was not lost or markedly attenuated due to blockage of the retrograde catheter.

Additional records of random pressure and flow signals were obtained just before (base line) and just after (response) two exposures to an aerosolized histamine diphosphate solution (Sigma). For the histamine exposures a stock solution of 5.0 mg histamine base/ml normal saline was prepared and diluted to give an additional concentration of 2.5 mg/ml. The selected concentration was placed in a Wright nebulizer driven with an airflow of 10 l/min, and the resulting aerosol was collected in a meteorological balloon. The aerosol was delivered to the animal through the endotracheal tube with a self-inflating breathing bag whose input was connected to the balloon. A total of 10 tidal breaths of the aerosol were delivered over a 30- to 40-s interval. Measurements of total and peripheral impedance were made during the first minute after the exposure. A recovery period of 15–20 min was allowed between exposures.

At the end of the experiment the animal was killed with an intracardiac injection of potassium chloride. With the retrograde catheter still in place the lungs were removed, inflated to a pressure of 5 cm formalin, and fixed. The lungs were later dissected to determine the location of the catheter and to evaluate tissue damage caused by insertion of the retrograde catheter. This postmortem examination was not performed on one dog.

The recorded pressure and flow signals were processed using spectral analysis techniques on a Digital Equipment MINC-11 computer (11, 20, 30). The applied pressure and flow signals were sampled at 512 Hz, and four consecutive sampled points were averaged so that the effective sampling rate was 128 samples/s. Thirty 1-s ensembles each containing 128 points were processed, and the results were averaged to obtain impedance data over the frequency range of 2–16 Hz (21). The resulting impedance data were corrected by subtracting the series impedance of the endotracheal tube at the appropriate power level to give total pulmonary impedance as a

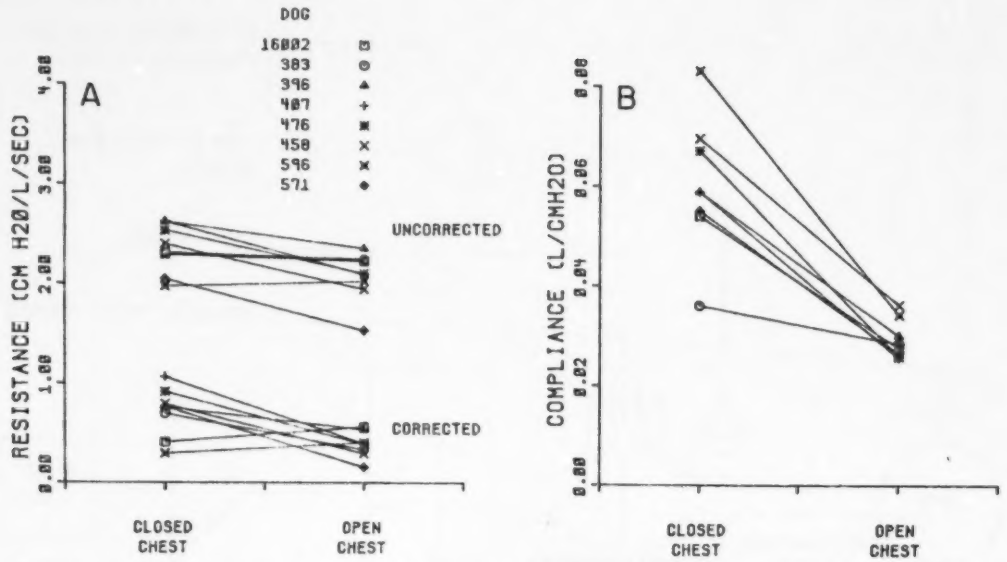


FIG. 2. Individual values of total resistance (*A*) and compliance (*B*) before and after opening chest. Resistance values after correction for endotracheal tube also are shown (*A*). Summary of statistical data is given in Table 1.

function of frequency over the range of 2–16 Hz (see APPENDIX). This impedance was expressed as real and imaginary parts representing the effective resistance and reactance, respectively. A least-squares parameter estimation technique was used to estimate values for resistance and compliance for a simple series model (28, 29). In a similar manner the retrograde catheter pressure signal and the flow signal were processed independently to obtain peripheral impedance data. No series correction was required for the peripheral data because the measured pressure did not include any endotracheal tube effects. The parameter estimation techniques were used again to obtain estimates of resistance and compliance, which in this case represented only the peripheral mechanical properties of the lungs.

RESULTS

Figure 2*A* shows individual values of the uncorrected total resistance with the chest both closed and open. Resistance values after correcting for the endotracheal tube also are shown. Table 1 gives mean values and standard errors of the estimate for closed-chest and open-chest resistance before and after correction for the series resistance of the endotracheal tube. The difference between the closed- and open-chest resistances was attributed to the resistance of the chest wall. For the uncorrected data this mean value was 0.28 ± 0.08 (SE) $cmH_2O \cdot l^{-1} \cdot s$, and for the corrected data the mean value was 0.33 ± 0.10 $cmH_2O \cdot l^{-1} \cdot s$. The difference between these values was not statistically significant.

Figure 2*B* shows individual values of total compliance with the chest both closed and open. Mean values and standard errors of the estimates for these conditions are given in Table 1. Mean values of open- and closed-chest compliances (C) were used to calculated the chest wall compliance using

$$1/C(\text{chest wall}) = 1/C(\text{closed chest}) - 1/C(\text{open chest})$$

The resulting value for the chest wall compliance was 0.0572 $l \cdot cmH_2O^{-1}$. This equation is analogous to that relating the value of one capacitor in a series combination to that of the other capacitor and the equivalent capacitance of the two in series.

Table 2 shows the location of the retrograde catheter in seven of the eight dogs. No postmortem examination was performed on *dog 396* because the catheter was inadvertently pulled out during the removal of the lungs. Table 2 gives the lobe in which the catheter was located and the number of bronchial orifices from the catheter to the trachea. With the exception of *dog 596* all catheters were clear, and only minimal trauma was noted at the catheter sites. In *dog 596* a significant hemorrhage occurred, making it an unacceptable preparation. The de-

TABLE 1. *Resistance and compliance in open and closed chest*

	Resistance, $cmH_2O \cdot l^{-1} \cdot s$		Compliance, $l \cdot cmH_2O^{-1}$
	Uncorrected	Corrected	
Closed Chest	2.35 ± 0.09	0.71 ± 0.08	0.0294 ± 0.0013
Open Chest	2.07 ± 0.09	0.39 ± 0.03	0.0603 ± 0.0045

Values are means ± SE.

TABLE 2. *Location of retrograde catheter*

Dog	Wt, kg	Lobe	Bronchial Orifices to Trachea
16,002	21	Not recorded	7
571	18.5	Rt lower	6
476	18	Rt middle	6
458	20	Rt middle	4
407	19.5	L lower	6
596*	18	Rt middle	5
383	18	Rt middle	6
396	22.5		

* In *Dog 596* marked hemorrhage was noted at the catheter site.

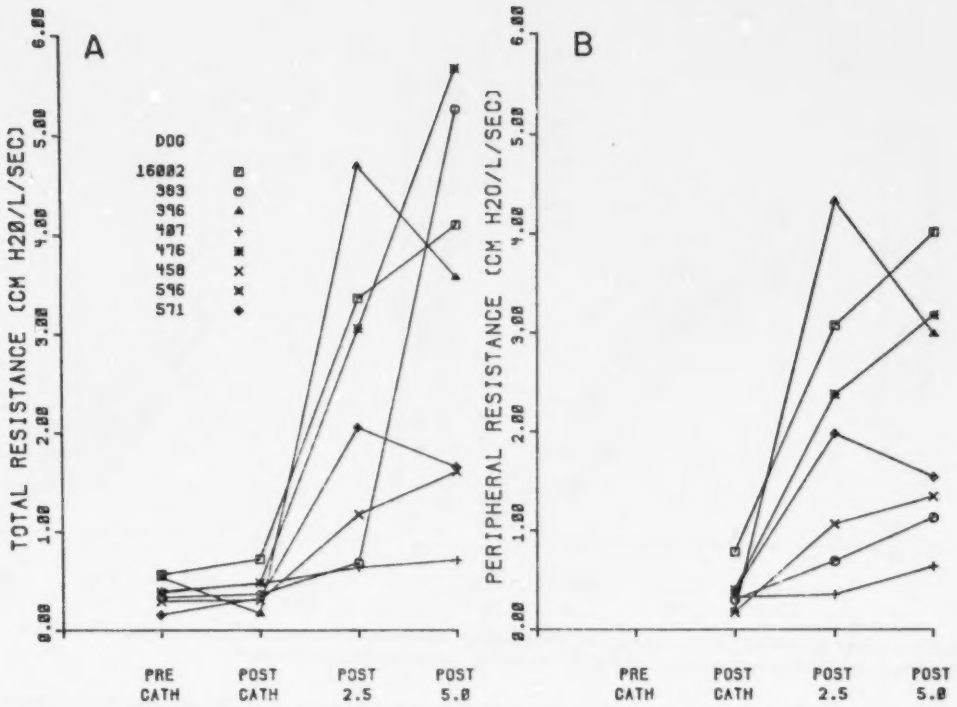


FIG. 3. Individual values of total (*A*) and peripheral (*B*) resistance before and after insertion of retrograde catheter and after inhalation of histamine aerosols of 2.5 and 5.0 mg/ml. Summary of statistical data is given in Table 3.

tection of marked changes in mechanical parameters after placement of the retrograde catheter in this dog supported this conclusion. Before insertion of the catheter, the total corrected resistance in *dog 596* was 0.406 $cmH_2O \cdot l^{-1} \cdot s$, and after insertion it increased to 1.847 $cmH_2O \cdot l^{-1} \cdot s$. Similarly, catheter insertion reduced total compliance from 0.082 to 0.047 $l \cdot cmH_2O^{-1}$. These changes were substantially larger than those observed in the other seven dogs (see Tables 3 and 4 below). In addition, the peripheral resistance in this dog after catheter insertion was 1.605 $cmH_2O \cdot l^{-1} \cdot s$, also substantially larger than values measured in the other dogs. For these reasons this dog was excluded from the average values reported below in Tables 3–5. However, the data for this dog were included in Figs. 2–4 and may be identified using the symbol legend on each figure.

With the chest opened the real part of the total impedance data (after correction for the series impedance of the endotracheal tube) was a measure of total pulmonary resistance. Individual values obtained for the eight dogs prior to insertion of the retrograde catheter, at base line after insertion of the catheter, and after exposure to concentrations of 2.5 and 5.0 mg/ml histamine aerosol are shown in Fig. 3*A*. For clarity of presentation we omitted the intermediate base-line values between the two exposures. However with the exception of *dog 383* whose intermediate base-line total resistance increased by 0.841 $cmH_2O \cdot l^{-1} \cdot s$, all dogs returned to a resistance within 0.282 $cmH_2O \cdot l^{-1} \cdot s$ of their earlier base-line values. The mean difference between the two base-line values was 0.166 $cmH_2O \cdot l^{-1} \cdot s$. Table 3 shows mean values and

TABLE 3. *Effect of retrograde catheter and histamine on resistance*

	Precatheter Base Line	Postcatheter Base Line	Posthistamine (2.5 mg/ml)	Prehistamine (5.0 mg/ml)	Posthistamine (5.0 mg/ml)
Total pulmonary resistance	0.382 ±0.049	0.407 ±0.061	2.239 ±0.537	0.573 ±0.100	3.225 ±0.204
Peripheral pulmonary resistance		0.367 ±0.071	1.977 ±0.494	0.489 ±0.052	2.115 ±0.441
Central pulmonary resistance		0.040 ±0.031	0.262 ±0.079	0.084 ±0.129	1.110 ±0.352

Values are means ± SE expressed in $cmH_2O \cdot l^{-1} \cdot s$. *Dog 596* was excluded from these values.

standard errors for all conditions including the intermediate base-line data. The post insertion base-line resistances ranged from 0.172 to 0.722 $cmH_2O \cdot l^{-1} \cdot s$ with a mean value of 0.407 $cmH_2O \cdot l^{-1} \cdot s$ when *dog 596* was excluded. All dogs responded to the histamine exposure, but the degree of response varied considerably. For example, in *dog 407* (represented by the symbol +) the total pulmonary resistance increased 78%, whereas in *dog 476* (represented by the symbol *) it increased 1,400%.

In a similar manner the real part of the peripheral impedance data was a measure of the peripheral resistance. Figure 3*B* shows peripheral resistance data obtained during the postcatheter base-line period and after inhalation of histamine aerosols of 2.5 and 5.0 mg/ml. Again the intermediate base-line data are omitted for clarity. Table 3 shows mean values and standard errors

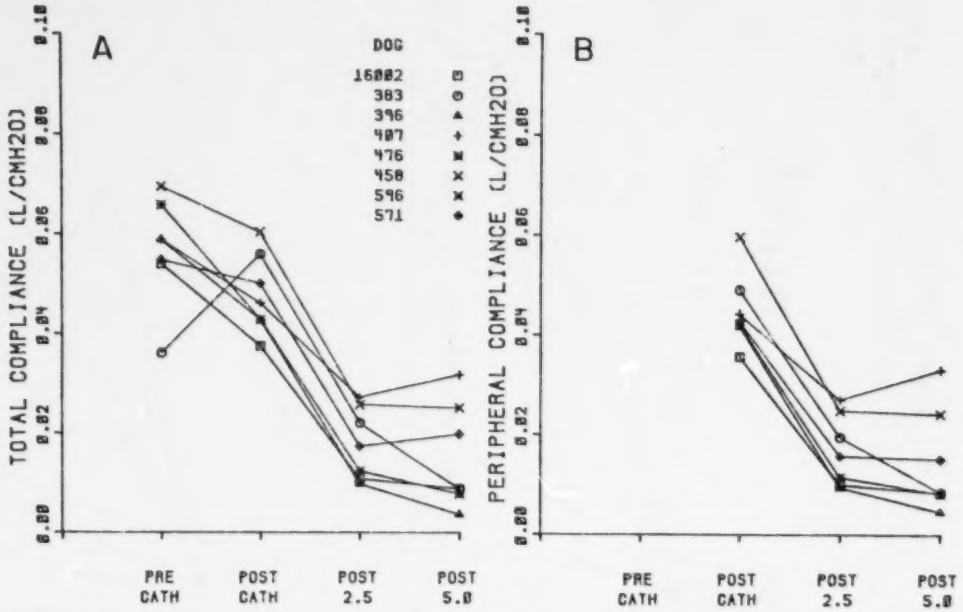


FIG. 4. Individual values of total (*A*) and peripheral (*B*) compliance before and after insertion of retrograde catheter, and after inhalation of histamine aerosols of 2.5 and 5.0 mg/ml. Summary of statistical data is given in Tables 4 and 5.

of the estimate for peripheral resistances for all conditions. At the lower histamine dose the average peripheral resistance increased 1.61 $cmH_2O \cdot l^{-1} \cdot s$ (439%). The average central resistance, obtained by subtracting the peripheral resistance from the total resistance, increased 0.222 $cmH_2O \cdot l^{-1} \cdot s$ (555%). Thus at the low histamine dose the response appeared to be more peripheral than central. After the higher histamine dose, the peripheral resistance increased 1.626 $cmH_2O \cdot l^{-1} \cdot s$ (333%) and the central resistance increased 1.026 $cmH_2O \cdot l^{-1} \cdot s$ (1,220%). In contrast to the lower dose of histamine, the higher dose produced substantial increases in both central and peripheral resistance.

Estimates of lung compliance and peripheral compliance were obtained by processing the imaginary part of the open-chest impedance data using regression analysis (28, 29). A correction for the reactance of the endotracheal tube was made prior to estimating lung compliance. No correction for endotracheal tube reactance was made for the peripheral compliance because the endotracheal tube impedance was not included in the peripheral measurements. Fig. 4 (*A* and *B*) shows individual values of the total and peripheral compliance values precatheter, postcatheter, and after 2.5 and 5.0 mg/ml histamine aerosol exposures. Table 4 shows mean values and standard errors of the estimates of lung compliance for all conditions. On the average, lung compliance decreased 15% following insertion of the peripheral catheter. Both lung compliance and peripheral compliance decreased by 62% following exposure to the 2.5 mg/ml histamine aerosol and recovered to 82% of their respective postcatheter values before the 5.0-mg/ml histamine exposure. After the 5.0-mg/ml histamine exposure both lung and peripheral compliance decreased by approximately 62% of their respective intermediate base-line values. These postexposure values of compliance were approximately 15% lower than those following the 2.5 mg/ml exposure.

Because the airway compliance was in parallel with the peripheral compliance (19), the difference between the lung and peripheral compliances provided a measure of the compliance of the central airways. Table 5 presents the difference between the base-line open-chest lung and

TABLE 4. *Effect of retrograde catheter and histamine on compliance*

	Precatheter Base Line	Postcatheter Base Line	Posthistamine (2.5 mg/ml)	Prehistamine (5.0 mg/ml)	Posthistamine (5.0 mg/ml)
Total lung compliance	0.0568 ±0.0038	0.0480 ±0.0028	0.0179 ±0.0025	0.0392 ±0.0021	0.0151 ±0.0037
Peripheral lung compliance		0.0450 ±0.0027	0.0169 ±0.0025	0.0374 ±0.0021	0.0146 ±0.0036

Values are means ± SE expressed as $l \cdot cmH_2O^{-1}$. *Dog 596* was excluded from these values.

TABLE 5. *Airway compliance before and after histamine aerosol*

Dog	Base-Line Compliance, $l \cdot cmH_2O^{-1}$	Posthistamine (2.5 mg/ml)
16002	0.00190	0.00080
383	0.00690	0.00250
396	0.00120	0.00040
407	0.00200	0.00020
476	0.00070	0.00090
458	0.00072	0.00090
571	0.00800	0.00160
Mean	0.00306	0.00104
±SEE	±0.00107	±0.00026

peripheral compliances for each dog prior to the first exposure to histamine aerosol and following exposure to the low dose of histamine aerosol (2.5 mg/ml concentration). For base-line data the mean value of the differences gave an airway compliance of 0.00306 $l \cdot cmH_2O^{-1}$, or approximately 6% of the total compliance. This value was in reasonable agreement with Mead's estimate of 2–3% in humans, and it agreed fairly well with the generally assumed value of 0.005 $l \cdot cmH_2O^{-1}$ (19). After exposure to the low dose of histamine the mean difference gave a value of 0.00104 $l \cdot cmH_2O^{-1}$. This was approximately 34% of the base-line value of airway compliance and implied a stiffening of the central airways in response to histamine. With the higher histamine dose (5.0 mg/ml) the difference between the average lung compliance and average peripheral compliances (Table 4) became 0.0005 implying further stiffening of the large airways. This finding was consistent with the larger increase in central resistance following the 5.0-mg/ml histamine exposure.

DISCUSSION

Previously our laboratory has reported several studies in which we used a sequence of single-frequency impedance measurements to compute resistance and compliance parameters in dogs (9, 24, 25, 29). Data obtained with the random noise technique in the present study were consistent with these previously reported data. Values of total resistance and compliance obtained with random noise while the chest was intact were similar to those previously computed from impedance data obtained from a sequence of single-frequency measurements (9, 24, 25, 29). From the open- and closed-chest random noise measurements we computed estimates of the chest wall resistance and compliance. The mean value of chest wall resistance obtained from uncorrected data in the present study, 0.328 $cmH_2O \cdot l^{-1} \cdot s$, agreed with the value reported by Haddad et al. (9), 0.40 $cmH_2O \cdot l^{-1} \cdot s$. The mean value of chest wall compliance in the present study, 0.057 $l \cdot cmH_2O^{-1}$, was approximately one-half that obtained in the single-frequency study (9) when the one outlying data point in the earlier study was removed. However the present mean value for chest wall compliance compared favorably with the value predicted using Spells' (27) regression equations. For a 19.5-kg dog (the mean weight of our dogs) the predicted value for chest wall compliance obtained from the regression equation was 0.068 l/cmH_2O^{-1}.

Several groups have used the Macklem and Mead retrograde catheter technique to partition resistance in dogs during an assortment of physiological and pharmacological interventions (12, 18, 31, 32, 33). Other investigators have used intrabronchial catheters to partition resistance (3, 13). Table 6 summarizes reported mean values of total, central, and peripheral lung resistance at a lung volume approximating FRC. These data are arranged in order of the peak-to-peak flow rate at which the measurements were made. Fig. 5 (*A* and *B*) shows graphical representations of the central and peripheral resistance data, respectively. The mean value for peripheral resistance resistance obtained in the present study, 0.367 $cmH_2O \cdot l^{-1} \cdot s$, indicated by the open circle in Fig. 5*B*, was well within the reported range. On the other hand, the mean value of the corrected central resistance, 0.040 $cmH_2O \cdot l^{-1} \cdot s$, indicated by the open circle in Fig. 5*A*, is substantially lower than those reported by others. We attributed most of this large difference to an overcorrection for the resistance of the endotracheal tube. In our study we corrected for the effects of this tube by subtracting the independently measured resistance of the endotracheal tube from the measured value at each frequency (see APPENDIX). Recently Chang and Mortola (1) showed that this correction technique effectively may overcorrect due to fluid mechanical factors resulting from the abrupt change in diameter at the end of the endotracheal tube. An effective overcorrection of 20% in our study could account for the low value of central resistance. This would mean that the effective overcorrection was nominally 0.33 $cmH_2O \cdot l^{-1} \cdot s$, 20% of the nominal value of the endotracheal tube resistance. If this were the case, the true mean value for the corrected central resistance would be near 0.37 $cmH_2O \cdot l^{-1} \cdot s$, which is in line with the values reported by others at low flow rates. Since 20% is well within the range of overcorrection reported by Chang and Mortola (1), we believe that this explains our low values of central resistance. It should be pointed out that this problem does not exist with the peripheral measurements, because the endotracheal tube was not in the measurement path and no correction was required.

Although the values for total and central resistance obtained in the present study seem to be low because of an overcorrection for the effects of the endotracheal tube, it also is possible that the results obtained in previous studies are somewhat high because of failure to account for the resistance of the tracheal cannula. Only Drazen et al. (3) and Irvin et al. (13) indicated that the resistance of the cannula had been taken into consideration. Drazen et al. (3) measured the resistance of the cannula used in their experiments, found it to be less than 0.05 $cmH_2O \cdot l^{-1} \cdot s$, and chose not to correct for its resistance. The inclusion of the cannula resistance in the reported values of total and central resistance should result in an overestimation of these values. The magnitude of the overestimation should be larger at the higher flow rates, because the resistance of the cannula should increase with increasing flow. Spells (27) in his literature survey

TABLE 6. *Previously reported mean values of total, central, and peripheral resistance*

Reference	Total Lung Resistance	Central Resistance	Peripheral Resistance	Peak-to-Peak Flow
Hoppin et al. (12)	0.89	0.54	0.34	0.2
Drazen et al. (5)	0.85	0.54	0.30	0.5
Fullton	0.41	0.04	0.37	0.6
Irvin et al. (13)	0.71	0.49	0.22	0.75
Wood et al. (31)	1.57	1.08	0.49	1.0
Macklem et al. (18)	1.9	1.55	0.35	1.5
Woolcock et al. (33)	1.16	0.996	0.20	1.5
Woolcock et al. (32)	1.95	1.76	0.19	1.5
Macklem and Mead (17)	1.75	1.5	0.25	1–2

Resistance is expressed as $cmH_2O \cdot l^{-1} \cdot s$, and flow as $l \cdot s^{-1}$.

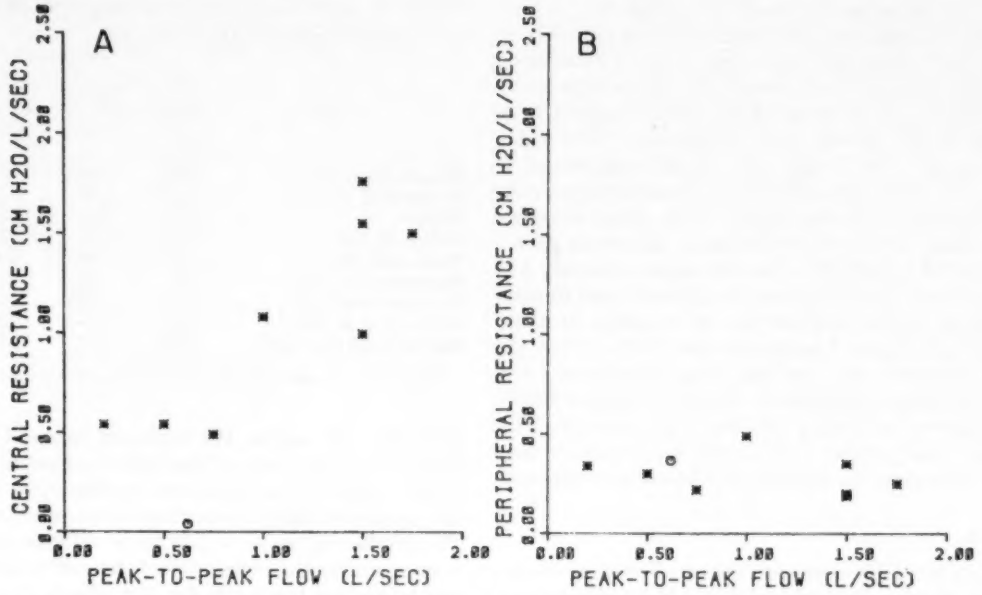


FIG. 5. Values for central (*A*) and peripheral (*B*) resistance at functional residual capacity obtained in other studies plotted as a function of peak-to-peak flow at which measurements were made. Results from present study are shown as *open circles*. Numerical data are shown in Table 6.

also found that most authors were not definite as to whether or not the cannula resistance had been subtracted. In two cases in which it was measured, the cannula resistance was found to be 13 and 24% of the measured resistance.

The data in Table 6 and Fig. 5 suggest that peripheral resistance is relatively independent of flow rate, whereas central resistance increases with the flow rate. We attributed this finding to the generally accepted notion that flow in the large central airways is more disturbed than flow in the small peripheral airways (22, 23, 26, 31) and to the fact that our peripheral resistance included the viscous resistance of the lung tissue, which would not be flow related. Previously, Wood et al. (31) found that resistance was independent of flow in airways whose diameter was 4 mm or less. However, in the larger airways resistance varied with flow rate and appeared to be proportional to flow to the 0.5 power. Wood et al. (31) pointed out that their results were consistent with flow resistance determined by the equation of boundary layer growth in the central airways and Poiseuille flow in the peripheral airways. In a similar vein, Drazen et al. (3, 4) found that peripheral resistance was relatively constant with a 100-fold increase in Reynolds number, while central resistance changed by a factor of 100 over the same range. This suggests that studies fractionating total resistance into central and peripheral components should report the flow rate at which the measurements were made.

We were able to obtain estimates of airway compliance in dogs by subtracting the peripheral compliance from the total lung compliance. In the control condition we obtained a mean value of 0.00306 $l \cdot cmH_2O^{-1}$. This value was in reasonable agreement with the generally accepted value of 0.005 $l \cdot cmH_2O^{-1}$ (19). We are unaware of any direct measurements of airway compliance. However, many groups have reported values for specific airway compliance based on measurements of diameter or area changes (2, 7, 10, 15, 16). Specific compliance values for the trachea ranged from 0.01 to 0.03 cmH_2O^{-1}, while values for the bronchi were larger. For example, Dawson and Elliot (2) reported values of 0.11 and 1.0 cmH_2O^{-1} for medium and small bronchi, respectively. It is difficult to relate these values to ours because the resting volume of the airways in our animals is unknown as is the distribution of this volume between the bronchi and the portion of the trachea distal to the endotracheal tube. However, if we divide our mean value by 0.08 l, a nominal value for dead space in dogs, we obtain a specific compliance of 0.038 cmH_2O^{-1}, which agrees with previously reported values in that it lies between the reported ranges for the trachea and bronchi.

Observed changes in airway compliance following histamine exposure also were consistent with changes reported by others following vagal stimulation and inhalation of acetylcholine (10, 16). After exposure to 2.5 mg/ml histamine aerosol, the mean value was 0.00104 $l \cdot cmH_2O^{-1}$, approximately one-third of the base-line value. At the higher histamine dose (5.0 mg/ml), the difference between the mean values for total and peripheral compliance suggested an additional decrease in airway compliance to 0.005 $l \cdot cmH_2O^{-1}$. However this value may be suspect because its magnitude was within the noise of the measurement and the standard error of the mean was relatively large.

The histamine-induced decrease in central airway compliance suggests some caution in interpreting a lack of frequency dependence in effective resistance or compliance following exposure to a bronchoconstricting agent. In previous reports, the presence or absence of

frequency-dependent behavior has been associated with the presence or absence of a preferential increase in peripheral resistance (6, 11, 19, 20, 30). These interpretations were based on Mead's model (19), which included a nonzero central airway compliance. In a stimulation study using this model we found that this compliance must be greater than 0.003 $l \cdot cmH_2O^{-1}$ to produce frequency-dependent behavior in the frequency range of 1–20 Hz as the peripheral resistance is increased. However, changes in frequency dependence did occur at higher frequencies when the airway compliance was smaller than this value. This simulation study suggests that the peripheral airways resistance can increase without producing frequency-dependent effects in a selected bandwidth if there is a corresponding stiffening of the central airways. The results of the present study support this suggestion. We found no change in the frequency dependence of the real part of the effective impedance in spite of directly measured increases in peripheral resistance, which were accompanied by increases in central resistance and decreases in central airway compliance. These results emphasize that frequency dependence in effective resistance or compliance indicates inhomogeneities in mechanical parameters and may not be present if substantial, but more or less uniform, changes have occurred.

Macklem and Mead (17) indicated that trauma caused by the introduction of the retrograde catheter should not affect the value of peripheral resistance because the resistance of the traumatized area was not being measured. We measured total resistance and compliance before and after insertion of the catheter. In one animal (*dog 596*) there was a substantial increase in total lung resistance and a corresponding decrease in total lung compliance after the catheter was inserted. Postmortem examination of this dog revealed a large hemorrhage in the vicinity of the catheter. It is difficult to attribute the approximately fourfold increase in resistance to a localized hemorrhage in the region of the catheter. It seems more likely that the trauma induced by placing the catheter caused a reflex change in the mechanical properties of the overall lung. Insertion of the retrograde catheter caused only minimal trauma in the other seven dogs. For these seven dogs there was a slight (6%) but statistically insignificant increase in the mean value of the total lung resistance following catheter insertion. There was also a slight (15%) but statistically insignificant decrease in total lung compliance. In most cases the placement of the catheter appeared to cause only small changes in the mechanical properties of the lung; however in some dogs much larger changes can occur. These can be detected by appropriate measurements of lung mechanics.

Although there was a wide range of responsiveness to inhalation of aerosolized histamine, the pattern of response was similar in all dogs. The lower dose (2.5 mg/ml) caused a predominantly peripheral response as indicated by approximately equal increases in the mean values of total and peripheral resistance and approximately equal decreases in the mean values of lung and peripheral compliances (Tables 3 and 4). More specifically the mean total resistance increased by 1.83 $cmH_2O \cdot l^{-1} \cdot s$, of which 1.61 $cmH_2O \cdot l^{-1} \cdot s$ (88%) was peripheral and 0.22 $cmH_2O \cdot l^{-1} \cdot s$ (12%) was central. Both total and peripheral compliance decreased by approximately 63%, whereas central compliance decreased by approximately 33%. These findings are in general agreement with those of Drazen et al. (5) who used dead-space measurements in conjunction with measurements of pulmonary conductance and dynamic compliance to study the effects of histamine aerosol on dogs. They found that the predominant effects of inhalation of aerosolized histamine were on the peripheral airways. At the higher dose (10.0 mg/ml) the response was somewhat different. The mean increase in peripheral resistance (1.62 $cmH_2O \cdot l^{-1} \cdot s$) was no larger than that observed with the smaller histamine concentration. However, the change in central resistance was 1.03 $cmH_2O \cdot l^{-1} \cdot s$, or 39% of the total change. Both total compliance and peripheral compliance once again decreased by approximately 62%, but the final values for both were approximately 15% less than at the lower dose, because intermediate base-line values were somewhat lower than initial base-line values. Thus the peripheral response was approximately the same for both histamine doses, but the central response was substantially greater following the larger dose.

In retrograde catheter studies the forced random noise approach offered some important advantages over the single-frequency approach. As previously mentioned, it provided a means for obtaining compliance estimates as well as resistance estimates. In addition it eliminated the necessity for manual manipulations to subtract the reactive portion of the pressure signal by electronically "closing the loop." These manipulations are computerized in the signal-processing techniques used in the random noise approach in that the pressure and flow signals are resolved into real (resistive) and imaginary (reactive) components as a function of frequency by the fast Fourier transform algorithm used to process the data. The random noise approach, which involves regression analysis, also has the advantage of effectively averaging measurements made at several frequencies over several time intervals, thereby providing better estimates. In addition, because many of the meaeasurements are away from the resonant frequency, small errors in the phase angles become less important (12).

The use of regression analysis with the forced random noise impedance data has one disadvantage in that frequency-dependent effects are averaged out of the data. This feature raises one question in the present study. Could a frequency dependence in total effective resistance or compliance, especially after histamine, lead to inaccurate values for the model parameters? The results of the simulation study mentioned above suggested that this was not a problem in the present study. In an analysis using the mean values of the measured parameters obtained during control and after the two histamine exposures, we found no changes in the frequency dependence of the simulated effective resistance or compliance among these three parameter sets. We were able to recover accurate values for total resistance and compliance by the use of regression analysis on the data derived from the simulation. Furthermore, we did not see any changes in the frequency dependence of the real part of the measured impedance following the two histamine doses. Thus we do not believe that the use of regression

analysis led to inaccurate interpretation of our data. However, in other simulation studies we have found that in cases where substantial frequency dependence of resistance and compliance is present, the use of linear regression techniques for parameter estimation may result in underestimation of parameter values.

APPENDIX

To define the correction for the endotracheal tube we made measurements using long records (100 s) at various flow rates. These data were interpreted using a series resistance-inertance model. The estimated inertance was independent of flow with a value of 0.06778 $cmH_2O \cdot s^2 \cdot l^{-1}$. The estimated resistance (R) was a function of both frequency (f) and root mean square flow rate ($\dot{Q}$), and these data were subjected to regression analysis using f and $\dot{Q}$ as independent variables. The resulting equation is

$$R(f) = (-0.12373 \cdot \dot{Q} + 0.009648) \cdot f + 6.0424 \cdot \dot{Q} + 0.62537 \quad (1)$$

Measured data were corrected by subtracting the appropriate value for the resistance of the endotracheal tube from the real part of the impedance data, and the reactance of the endotracheal tube from the imaginary part of the measured impedance. The appropriate resistance of the endotracheal tube at each frequency was found from *Eq. 1* using the RMS flow rate at which the measurement was made. The reactance of the endotracheal tube was given by $6.28318 \cdot f \cdot I$ where I was the estimated inertance of the endotracheal tube given above.

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